

Review

The Orphan Nuclear Receptors, Estrogen Receptor-related Receptors: their Role as New Biomarkers in Gynecological Cancer

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Abstract. *The family of estrogen receptor-related receptors (ERRs) is a subfamily of the orphan nuclear receptors, which is closely related to the estrogen receptor (ER) family. Research on ERRs has shown that the ERR family share target genes, co-regulators and promoters with the ER family. ERRs seem to interfere with the classic ER-mediated estrogen responsive signaling in various ways. Moreover, ERRs have been reported to be prognostic biomarkers in breast, ovarian and colorectal cancer. ERRs should be considered as additional factors in the evaluation of gynecological tumors. Since ERRs have an important influence on the overall estrogenic response, they are of clinical importance in gynecological cancer, but also regarding women's general health.*

Estrogens have important physiological functions in the proper development, sexual differentiation and maintenance of both the female and male reproductive systems. Abnormal estrogen activity has been connected with numerous diseases, including osteoporosis, coronary heart disease, as well as some estrogen-related malignancies such as breast, endometrial and ovarian cancer (1). The pleiotropic effects of estrogen are mediated by two classic estrogen receptors known as ER α and ER β

(according to the American Nuclear Receptors Nomenclature Committee 1999, named as NR3A1 and NR3A2) (2), which are ligand-activated transcription factors (2, 3). As members of the nuclear receptors (NRs), ERs regulate the target gene expression by recruiting co-regulators to a specific DNA element, the estrogen response element (ERE) (4). However, not all of the estrogen response effects can be explained by this classic estrogen-ER-ERE signal transduction theory. There might be some bypass to the classic estrogen pathway or a co-regulated mechanism in the estrogen-ER signal pathway.

Recently, some interesting results have been reported concerning orphan nuclear receptors, which also belong to the NRs superfamily. In contrast to the ligand-dependent definition, these NRs were activated in a constitutive manner without any known ligand (thus "orphan") (5-7). There is also a subfamily of orphan NRs closely related to the ERs, named estrogen receptor-related receptors (ERRs) (5). Due to their high homology with ERs, the members of the ERR family probably transduce signals by cross-talk with other NRs *via* common binding sites as well as ERR-specific binding sites. Ongoing studies have confirmed that various orphan NRs play an important role in the pathway of nuclear signal transduction and the regulation of gene transcription (7). In this review, the role of ERR in the estrogen-ER signal pathway and estrogen-related cancer are discussed.

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ERRs Gene Position and Structure

To date, the ERR subfamily is known to comprise the following members: ERR α , ERR β and ERR γ (NR3B1, NR3B2 and NR3B3, respectively), which also belong to group III of the NRs superfamily with ER, glucocorticoid

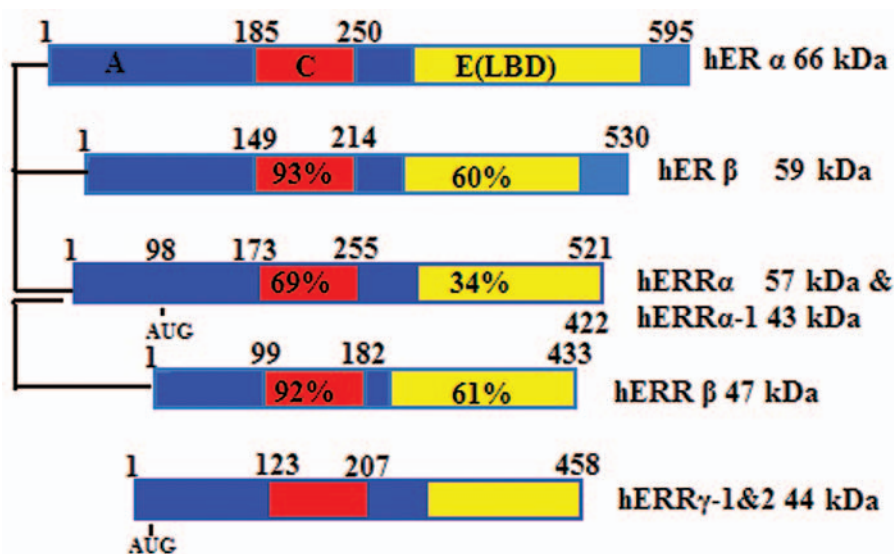


Figure 1. The human ER and ERR family. The percentage on the C domain (DBD) and E/F domain (LBD) indicated the different levels of similarity between isoforms of these two families. ER α and ER β have 93% and 60% identity in the DBD and LBD; respectively, ER α and ERR α have 69% (70% with ERR α -1) and 34% (35% with ERR α -1) identity, respectively; ERR α and ERR β have 92% and 61% identity, respectively (Refs. 2, 7, 34, 42, 55).

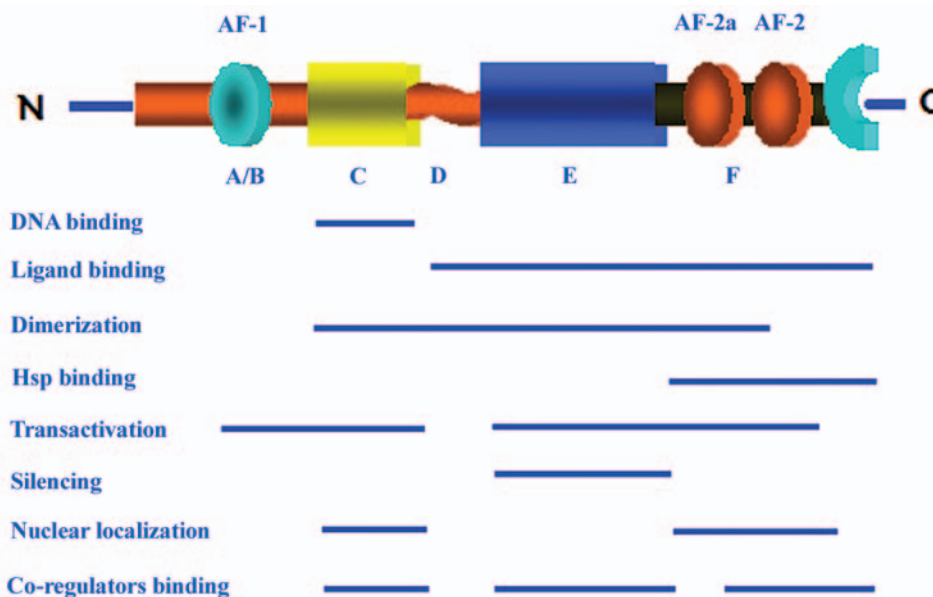


Figure 2. Scheme of the human ER and ERR family' structure and function. On ER, there is an F domain in the C terminal, which is poorly understood. The AF-2a transactivation domain is only for ER, and the AF-2 domain plays a very important role in the ERR function (Refs. 2, 7, 34, 42, 55).

receptor (GR; NR3C1), mineralocorticoid receptor (MR; NR3C2), progesterone receptor (PR; NR3C3) and androgen receptor (AR; NR3C4) (5, 8-10). ER α and ER β were first identified by low-stringency screening kidney cDNA libraries with a probe corresponding to the DNA-binding domain (DBD) of ER α , and named estrogen receptor-related receptors (ERRs) (5). ER γ , the third

member of the ERR subfamily, was identified 10 years later by two-hybridization screening with the glucocorticoid receptor-interacting protein 1 (GRIP-1) as a probe (8). Each member of the ERRs has isoforms (8, 10-12). A major isoform of ER α , ER α -1, was isolated from human endometrial carcinoma RI-95-2 cell line based on its binding to the steroid factor-1 responsive element (SFRE) (11).

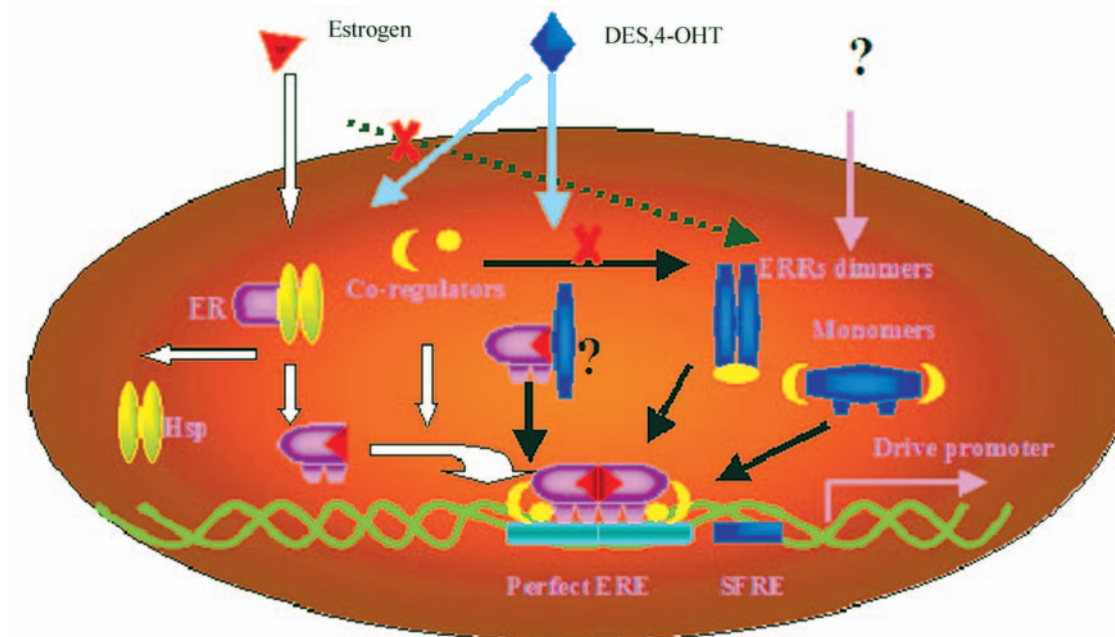


Figure 3. The intracellular interaction between ER and ERR. The classic E-ER signaling (white arrows): ER is activated by natural estrogen or synthetic estrogen (E) such as DES and 4-OHT. The E-ER complex then changes its structure to recognize and trigger the target gene expression following binding to ERE with co-regulators. Interference of ERR in E-ER signaling (black arrows): ERR can recognize not only the ERE, but also ERRE and SFRE in a constitutive manner or in dimers. ERR can compete with ER binding for ERE or co-regulators. DES and 4-OHT were reported to block the binding between co-regulators and ERR and to down-regulate ERR activity. Most mechanisms of the interaction between ER and ERR *in vivo* are still unclear.

Using fluorescence *in situ* hybridization (FISH), the gene encoding ERR α was mapped to chromosome 11q12-q13 and the ERR β gene was mapped to 14q24.3 (13, 14). The ERR γ gene was also identified on chromosome 1q41 (9). Analysis of the genomic organization and promoter characterization revealed that the nucleonic sequence adjacent to the transcription start sites of human ERR encoding gene lacks the typical TATA and CAAT boxes, but is GC-rich and contains 10 consensus Sp1-binding elements and 2 E boxes (13). The human genome also encodes an ERR-related pseudogene, which is located on chromosome 13q21. It was first reported as a pseudogene associated with a member of the orphan NRs family (14). All the ERRs display a high degree of sequence homology with their DBD and ligand-binding domain (LBD). The ER families also have a high degree of sequence homology with the ERR family (Figure 1), which strongly indicates that they probably bind to the same element on the target promoter and have an overlapping function.

As for conventional NRs, ERRs are organized into several modular regions, which have distinct biological functions (15-17) (Figure 2). The A/B regions are located at the N-terminus and include the activation function 1 (AF-1 region). The C region includes the DBD, which is the most evolutionarily conserved region and contributes to the special DNA-binding by the two zing-finger motif. The D

region is considered to be a hinge region, bridging the N-terminal and C-terminal. The E region contains the LBD, which contains the ligand-binding hydrophobic pocket and contributes to the receptors' dimerization. In ERs, there is a hormone-dependent transcription activation region (AF-2 region) embedded within the LBD. However, the functions of the D and the F domains are poorly understood.

Sequence analyses comparing all the NR3 families have shown that ERs and ERRs form the same branch of group III, which recognizes the hormone response element (HRE) sequence as 5'-AGGTCA-3', whereas the other four steroid receptors recognize the sequence as 5'-AGAACA-3' and form another branch (18). The genome of *Drosophila melanogaster* encodes a single member of this group, an ERR ortholog (19), indicating that all group III NRs might have originated from an ancestral ERR. ERR displays the same domain organization as classic receptors, which have been conserved through evolution, suggesting their critical role in the estrogen signal pathway.

Expression Pattern of ERR

ERR α appears to be widely distributed, both in the developing embryo and in adult tissue (20-22), although it is more abundant in the uterus (cell lines), prostate, brain (5), heart, skeletal muscle (13) and brown fat tissue (20).

During fetal mouse development, $ERR\alpha$ mRNA can be detected in the embryonic stem (ES) cells and in the development of the heart and skeletal muscle, the central and peripheral nervous system, the epidermis and the epithelium of the intestine and urogenital tract (23). This expression begins at the time of chorioallantois fusion in the placenta, through the development of heart, intestine, brain, spinal cord, brown fat and bone, thereby suggesting a primary role for this receptor throughout life. However, the mechanism of the $ERR\alpha$ function is still not completely understood. In contrast to the widespread expression patterns of $ERR\alpha$ and $ERR\gamma$, $ERR\beta$ is present early in the extra-embryonic ectoderm during the development of the placenta and $ERR\beta$ is also found at very low concentrations in a few specific tissues (kidney, heart, hypothalamus, hippocampus cerebellum, rat prostate, specific areas of the mouse brain) (5, 24-26). In mice lacking $ERR\beta$, trophoblast stem cell differentiation is impaired and the placenta fails to develop normally (25). $ERR\beta$ is also essential for reproduction and normal development. $ERR\gamma$ transcripts can be detected widely in the brain, lung, bone marrow, adrenal and thyroid glands, trachea and spinal cord, with very high levels in fetal brain and lower levels in the kidney and liver (8, 9). Recently, study on the expression of ERRs in the human placenta throughout gestation revealed that ERRs mRNA levels gradually increased up to the second trimester and then comparatively rapidly increased until normal term delivery, which indicated ERRs might be candidates for the interacting factors in human placental growth from the second trimester until normal term delivery (27).

ERR Function and Intracellular Interaction with ERs

Although the ERRs were discovered more than 10 years ago, knowledge regarding their biology and function is limited. Recent results have shown that the ERRs share target genes, co-regulatory proteins and DNA-binding sites with the ERs (11, 28-31). Despite the high degree of sequence similarity with ER construction, ERRs do not bind to the natural estrogens such as E_2 (32). The identification of naturally occurring ligands for ERR family members has remained elusive. However, silicone superimpositions of the ligand-binding pocket of $ERR\alpha$ and that of $ER\alpha$ have revealed a high level of local alanine residue sequence identity, suggesting that structurally close ligands could probably be bound by both receptors (33, 34). There are also reports suggesting that $ERR\alpha$ may have a natural ligand yet to be identified. The activity of $ERR\alpha$ -1 has been reported to be antagonized by two organochlorine pesticides and toxaphene (33, 35) and the activity of $ERR\alpha$ -1 showed signs of being dependent on an

unidentified serum component (32). Des (diethylstilbestrol) appeared to inactivate all three members (36), while 4-OHT (4-hydroxytamoxifen) seemed to bind only to $ERR\beta$ and $ERR\gamma$ and selectively inactivate $ERR\gamma$ in cell-based assay (37, 38). Strikingly, all these compounds have been associated with estrogen signaling and shown repression of ERRs' transcriptional activities. They can thus be considered as antagonists (if ERRs possess natural ligands) or inverse agonists (if ERRs' transcriptional activities are constitutive) (34). Recently, the PPAR γ coactivator 1 α (PGC1 α) and 1 β (PGC1 β) were reported to be the potential ERR ligands and *in vitro* were found to contribute to control the energy balance (39, 40).

ERR monomers preferably recognize the consensus extended half-site 5'-TnA-AGGTCA-3' with a high-affinity, referred to as the ERR-responsive element (ERRE) (11, 18, 20, 41). This class of binding site is also recognized by the monomeric orphan NR steroidogenic factor-1 (SF-1; NR5A1), a regulator of the steroid biosynthesis pathway also essential for the development of the hypothalamic-hypophyseal-adrenocortical axis (22). The members of the ERR family can recognize variants of ERE, including the perfect ERE, ERRE and SFRE, imperfect ERE (34, 42) and TREpal (palindromic thyroid hormone responsive element) (43) by dimers or monomers. Though the activation mechanisms of ERR remain totally unknown, the ERRs need to recruit the co-regulatory protein to maintain their function. ERRs were observed to compete with ER in binding to the steroid receptor co-activator (SRC) family, highly essential for the ER-mediated gene transcription, the integration of intracellular signaling pathways and control of the cell cycle (42). On the other hand, in the absence of exogenous factors, all the ERRs have been shown to interact with some co-activators and activate gene transcription in a constitutive manner (8, 18, 21, 28, 29, 44). Thus, ERR may play an important role in the response of some estrogen-responsive genes *via* heterodimerization with ERs or in direct competition with ERs for binding to ERE or co-activators (12, 30, 43, 45). $ERR\alpha$ -1 can act as a modulator of estrogenic responses, functioning as either an active repressor or a constitutive activator in estrogen-dependent transcription. Although the transcriptional activities of ERR are not regulated by estrogens nor by any identified natural ligand (34), the expression of $ERR\alpha$ has been suggested to be regulated in mouse uterus (46). Furthermore, ERRs can actively influence the function of estrogenic responsive genes, suggesting that there is a key way that ERRs regulate the estrogen-ER signal pathway, although the mechanism of this cross-talk between these two receptor subfamilies is still not clear. These observations offer additional layers of regulatory complexity to the intracellular interaction between ERRs and ERs (Figure 3).

In the context of transcription factors and co-regulators, the ERRs regulate the target gene activity in a ligand-, cell type-, responsive element- and promoter context-specific manner. ERRs play an active role in bone morphogenesis by regulating the osteopontin gene, bone resorption and osteoprogenitor cell proliferation and differentiation (47). $ERR\alpha$ regulates the transcriptional activity of the human lactoferrin gene (11, 45), the human medium-chain acyl coenzyme A dehydrogenase gene (20, 48), the thyroid receptor α gene (22), the aromatase gene (49, 50), the osteopontin gene (50, 51) and the small heterodimer partner (SHP) gene (44). The major isoform of the human $ERR\alpha$ gene, $ERR\alpha 1$, can sequence-specifically bind to a consensus palindromic ERE and directly compete for binding with the $ER\alpha$. $ERR\alpha 1$ activates or represses ERE-regulated transcription in a cell type-dependent manner, repressing the ERE-mediated transcriptions in ER-positive MCF-7 cells, while activating the ERE-mediated transcriptions in ER-negative HeLa cells (31). Expression of $ERR\alpha$ was also reported under circadian regulation in estrogen-responsive tissues as an output gene of the circadian clock oscillator (52). $ERR\beta$ functions as a potent cell-specific, receptor-specific repressor of transcriptional activity mediated by a glucocorticoid receptor (53). The expression of two isoforms of mouse $ERR\gamma 1$ and $ERR\gamma 2$ in the central nervous system during embryonic development and in the brain of the adult mouse suggests that they may take part in the differentiation and function of the brain (54). Although numerous interconnections between ERR and estrogen signaling have been documented and are discussed in recently published reviews (34, 42, 55), little is known about the *in vivo* function of ERR.

ERRs in Estrogen-related Cancer

The breast, uterus and the ovary are considered as the classic estrogen target organs. ERs are highly expressed in these tissues and their malignancies. In estrogen-related cancers, $ER\alpha$ mediates estrogen-responsive cell proliferation and plays a crucial role in their etiology (56, 57). Thus, the malignant mechanisms of these tissues were found to be rate-limited by estrogen-ER signal pathways. $ER\alpha$ has been established as the single most important genetic biomarker and target for cancer therapy, especially in breast and endometrial carcinoma. Selection of patients with ER-positive expression increases the endocrine therapy responsive rates based on anti-estrogen (58). However, not all anti-estrogen therapies are effective for ER-positive patients. On the other hand, the status of some patients without ER expression can be improved by the combination of anti-estrogen and progesterone agonist treatment. This suggests some other net-regulation between the estrogen nuclear signal pathways.

Research on mammary carcinoma cell and cervical cancer showed that both $ER\alpha$ and $ERR\alpha 1$ can bind to the palindromic ERE sequence and that there is competition between these two nuclear receptors (30, 31). It was confirmed that the pS2 gene, a human breast prognostic marker, whose promoter has an ERE, can be regulated by the ERRs as a target gene (29). Consensus ERE were reported in several target genes including: lactoferrin, pS2, c-fos, c-jun, c-myc and EGF receptor, epidermal growth factor, cyclin D1 and the breast cancer-1 (BRCA-1) gene (55). These genes are potential target genes regulated by the ERRs base on their ability to bind to variant ERE. Using two-yeast hybridization and electrophoretic mobility shift analysis (EMSA), $ERR\gamma$ was reported to recognize a tremendously broad range of sequences as a homodimer (59). Therefore, ERRs may play an important role in the etiology of some estrogen-related cancer.

Recently, the *in vitro* and *in vivo* role of ERRs was studied in human breast carcinoma (5, 58, 60), endometrial carcinoma cells (30, 45) and ovarian cancer (61). Moreover, ERRs were also analyzed in the human prostate including cell lines and tissues (62) and colorectal tumor (63). Abnormal estrogen synthesis was considered to be a major inducing factor for the development of estrogen-related cancer. To adjust estrogen synthesis, aromatase activity was the most important limiting step. The promoters I.3 and II are thought to be important in driving abnormal aromatase expression/estrogen synthesis in breast tumor. A regulatory element (S1) behaves either as an enhancer or repressor between these two promoters. $ER\alpha$ can bind to the S1 element and repress the aromatase promoter activity as a feedback mechanism to suppress abnormal estrogen biosynthesis, whereas $ERR\alpha$ was found to be the major protein interacting as an enhancer with the silence element (S1) of the human aromatase gene in breast tissue (64). Its ability to interact with $ER\alpha$ and to modulate aromatase expression/estrogen biosynthesis suggests that $ERR\alpha$ plays a critical role in normal breast development and in the pathogenesis of breast cancer (49). Furthermore, the non-classic estrogenic stimulation derived from $ERR\alpha$ is associated with mitogen-activated protein kinases (65). The importance of ERRs in human breast cancer was also assessed by comparing their mRNA profiles with established clinically pathological indicators and the mRNA profiles of ERs and ErbB family members (58). $ERR\alpha$ may be an important unfavorable marker in a significant proportion of patients with breast cancer, because the tumors containing the highest levels of $ERR\alpha$ were associated with a steroid receptor-negative status and hormonal insensitivity. $ERR\alpha$ status might be useful as a positive marker to predict the sensitivity of ErbB-2-based therapy, such as Herceptin (58). Furthermore, ERR expression in breast cancer tissue is limited to the tumor

epithelium rather than to the surrounding adipose stroma (60). However, ERR γ shows potential as a favorable marker of clinical course. In ovarian cancer, the expression of ERR α was associated with shorter overall survival and the expression of ERR γ was observed with a longer progression-free survival (61). Moreover, ERR α seems to emerge as a novel potential modifier of the malignant colorectal tract because the change in the expression of ERR α mRNA is associated with tumor progression or with different histopathological stage of the cancer (63). In general, ERRs play important roles in estrogen-related cancer; ERR α and ERR γ are potential targets for new therapeutic developments.

Conclusion

ERRs are important pleiotropic modulators of ER-mediated target genes and ERR-specific gene transcription. The contribution of ERRs to estrogen signaling is known and the search for potential ligands and new target genes should be of primary importance in the future. The major goals of future studies should be to directly identify the ER and ERR target genes, using technologies such as chromatin immunoprecipitation assays and gene arrays. The regulation of these genes should also be confirmed by each receptor subtype in both cell- and animal-based models. These objectives should include: the identification of the target genes regulated by the ERR family; the functions of ERR in estrogen-induced cancer; the evaluation of ERR as a therapeutic target, especially on estrogen-independent tumors; the relationship between ERR and SERM (select estrogen receptor modulator).

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References

- Turner RT, Riggs BL and Spelsberg TC: Skeletal effects of estrogen. *Endocr Rev* 15: 275-300, 1994.
- Muramatsu M and Inoue S: Estrogens receptors: how do they control reproductive and nonreproductive functions? *Biochem Biophys Res Commun* 270: 1-10, 2000.
- Watanabe T, Inoue S, Ogawa S, Ishii Y, Hiroi H, Ikeda K, Orimo A and Muramatsu M: Agonistic effect of tamoxifen is dependent on cell type, ERE-promoter context, and estrogen receptors α and β . *Biophys Res Commun* 236: 140-145, 1997.
- Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schutz G, Umesono K, Blumberg B, Kastner P, Mark M and Chambon P: The nuclear receptors superfamily: the second decade. *Cell* 83: 835-839, 1995.
- Giguere V, Yang N, Segui P and Evans RM: Identification of a new class of steroid hormone receptors. *Nature* 331: 91-94, 1988.
- Enmark E and Gustafsson JA: Orphan receptors – the first eight years. *Mol Endocrinol* 10: 1293-1307, 1996.
- Giguere V: Orphan nuclear receptors: from gene to function. *Endocr Rev* 20: 689-725, 1999.
- Hong H, Yang L and Stallcup MR: Hormone-independent transcriptional activation and coactivator binding by novel orphan nuclear receptors ERR3. *J Biol Chem* 274: 22618-22626, 1999.
- Eudy JD, Yao S, Weston MD, Ma-Edmonds M, Talmadge CB, Cheng JJ, Kimberling WJ and Sumegi J: Isolation of a gene encoding a novel member of the nuclear receptors superfamily from the critical region of Usher syndrome type II at 1q41. *Genomics* 50: 382-384, 1998.
- Chen F, Zhang Q, McDonald T, Davidoff MJ, Bailey W, Bai C, Liu Q and Caskey CT: Identification of two hERR2-related novel nuclear receptors utilizing bioinformatics and inverse PCR. *Gene* 228: 101-109, 1999.
- Yang N, Shigeta H, Shi HP and Teng CT: Estrogen receptor-related receptor, hERR-1, modulates estrogen receptor-mediated response of human lactoferrin gene promoter. *J Biol Chem* 271: 5795-5804, 1996.
- Heard DJ, Norby PL, Holloway J and Vissing H: Human ERR γ , a third member of the estrogen receptor-related receptor (ERR) subfamily of orphan nuclear receptors: tissue-specific isoforms are expressed during development and in the adult. *Mol Endocrinol* 14: 382-392, 2000.
- Shi H, Shigeta H, Yang N, Fu K, O'Brian G and Teng CT: Human estrogen receptor-like 1 (ESRL1) gene: genomic organization, chromosomal localization and promoter characterization. *Genomics* 44: 52-60, 1997.
- Sladek R, Beatty B, Squire J, Copeland NG, Gilbert DJ, Jenkins NA and Giguere V: Chromosomal mapping of the human and murine orphan receptors ERR α (ESRRA) and ERR β (ESRRB) and identification of a novel human ERR α -related pseudogene. *Genomics* 45: 320-326, 1997.
- Ham J and Parker MG: Regulation of gene expression by nuclear hormone receptors. *Curr Opin Cell Biol* 92: 222-232, 1989.
- Glass CK: Different recognition of target genes by nuclear receptor monomers, dimers and heterodimers. *Endocr Rev* 15: 391-407, 1994.
- Perlmann T and Evans RM: Nuclear receptors in Sicily: all in the famiglia. *Cell* 90: 391-397, 1997.
- Johnston SD, Liu X, Zuo F, Eisenbraun TL, Wiley SR, Kraus RJ and Mertz JE: Estrogen-related receptor- α 1 functionally binds as a monomer to extend half-site sequence including ones contained within estrogen-response elements. *Mol Endocrinol* 11: 342-352, 1997.
- Maglich JM, Sluder A, Guan X, Shi Y, McKee DD, Carrick K, Kamdar K, Willson TM and Moore JT: Comparison of complete nuclear receptor sets from the human, *Caenorhabditis elegans* and *Drosophila* genomes. *Genome Biol* 2(8): RESEARCH0029. Epub 2001 Jul 24.
- Sladek R, Bader JA and Giguere V: The orphan nuclear receptor estrogen-related receptor α is a transcriptional regulator of the human medium-chain acyl coenzyme A dehydrogenase gene. *Mol Cell Biol* 17: 5400-5409, 1997.

- 21 Bonnelye E, Vanacker JM, Dittmar T, Begue A, Desbiens X, Denhardt DT, Aubin JE, Laudet V and Fournier B: The ERR-1 orphan receptor is a transcriptional activator expressed during bone development. *Mol Endocrinol* 11: 905-916, 1997.
- 22 Vanacker JM, Bonnelye E, Delmarre C and Laudet V: Activation of the thyroid receptor- α gene promoter by the orphan nuclear receptor ERR α . *Oncogene* 17: 2429-2435, 1998.
- 23 Bonnelye E, Vanacker JM, Spruyt N, Alric S, Fournier B, Desbiens X and Laudet V: Expression of the estrogen related receptor-1(ERR-1) orphan receptor during mouse development. *Mech Dev* 65: 71-85, 1997.
- 24 Pettersson K, Svensson K, Mattsson R, Carlsson B, Ohlsson R and Berkenstam A: Expression of a novel member of estrogen response element-binding nuclear receptors is restricted to the early stages of chorion formation during mouse embryogenesis. *Mech Dev* 65: 1997.
- 25 Luo J, Sladek R, Bader JA, Matthyssen A, Rossant J and Giguere V: Placental abnormalities in mouse embryos lacking orphan nuclear receptor ERR β . *Nature* 388: 778-782, 1997.
- 26 Lorke DE, Susens U, Borgmeyer U and Hermans-Borgmeyer I: Different expression of the estrogen receptor-related receptor γ in the mouse brain. *Brain Res Mol Brain Res* 77: 277-280, 2000.
- 27 Fujimoto J, Nakagawa Y, Toyoki H, Sakaguchi H, Sato E and Tamaya T: Estrogen-related receptor expression in placenta throughout gestation. *J Steroid Biochem Mol Biol* 94: 67-69, 2005.
- 28 Xie W, Hong H, Yang NN, Lin RJ, Simon CM, Stallcup MR and Evans RM: Constitutive activation of transcription and binding of coactivator by estrogen-related receptors 1 and 2. *Mol Endocrinol* 13: 2151-2162, 1999.
- 29 Lu D, Kiriya Y, Lee KY and Giguere V: Transcription regulation of the estrogen-inducible pS2 breast cancer marker gene by ERR family of orphan nuclear receptors. *Cancer Res* 61: 6755-6761, 2001
- 30 Zhang Z and Teng CT: Estrogen receptor α and estrogen receptor-related receptor α 1 compete for binding and coactivator. *Mol Cell Endocrinol* 172: 223-233, 2001.
- 31 Kraus RJ, Ariazi EA, Farrell MI and Mertz JE: Estrogen-related receptor α 1 actively antagonizes estrogen receptor-regulated transcription in MCF-7 mammary cells. *J Biol Chem* 277: 248626-24834, 2002.
- 32 Vanacker JM, Bonnelye E, Chopin-Delannoy S, Delmarre C, Cavailles V and Laudet V: Transcriptional activities of the orphan nuclear receptor ERR α (estrogen receptor-related receptor- α). *Mol Endocrinol* 13: 724-733, 1999.
- 33 Chen S, Zhou D, Yang C and Sherman M: Molecular basis for the constitutive activity of estrogen-related receptor α -1. *J Biol Chem* 276: 28465-28470, 2001.
- 34 Horard B and Vanacker JM: Estrogen receptor-related receptors: orphan receptors desperately seeking a ligand. *J Mol Endocrinol* 31: 349-357, 2003.
- 35 Yang C and Chen S: Two organochlorine pesticides, toxaphene and chlordane, are antagonists for estrogen-related receptor α -1 orphan receptor. *Cancer Res* 59: 4519-4524, 1999.
- 36 Tremblay GB, Kunath T, Bergeron D, Lapointe L, Champigny C, Bader JA, Rossant J and Giguere V: Diethylstilbestrol regulates trophoblast stem cell differentiation as a ligand of orphan nuclear receptor ERR β . *Genes Dev* 15: 833-838, 2001.
- 37 Coward P, Lee D, Hull MV and Lehmann JM: 4-hydroxytamoxifen binds to and deactivates the estrogen-related receptor γ . *Proc Natl Acad Sci USA* 98: 8880-8884, 2001.
- 38 Tremblay GB, Bergeron D and Giguere V: 4-hydroxytamoxifen is an isoform-specific inhibitor of orphan estrogen-receptor-related (ERR) nuclear receptors β and γ . *Endocrinology* 142: 4572-4576, 2001.
- 39 Kamei Y, Ohizumi H, Fujitani Y, Nemoto T, Tanaka T, Takahashi N, Kawada T, Miyoshi M, Ezaki O and Kakizuka A: PPAR γ coactivator 1 β /ERR ligand 1 is an ERR protein ligand, whose expression induces a high-energy expenditure and antagonizes obesity. *Proc Natl Acad Sci USA* 100: 12378-12383, 2003.
- 40 Laganier J, Tremblay GB, Dufour CR, Giroux S, Rousseau F and Giguere V: A polymorphic autoregulatory hormone response element in the human estrogen-related receptor α (ERR α) promoter dictates peroxisome proliferator-activated receptor γ coactivator-1 α control of ERR α expression. *J Biol Chem* 279: 18504-18510, 2004.
- 41 Vanacker JM, Pettersson K, Gustafsson JA and Laudet V: Transcriptional targets shared by estrogen receptor-related receptors (ERRs) and estrogen receptor (ER) α but not by ER β . *EMBO* 18: 4270-4279, 1999.
- 42 Giguere V: To ERR in the estrogen pathway. *Trends Endocrinol Metab* 13: 220-225, 2003.
- 43 Luo X, Ikeda Y and Parker KL: A cell-specific nuclear receptor is essential for adrenal and gonadal development and sexual differentiation. *Cell* 77: 481-490, 1994.
- 44 Sanyal S, Kim JY, Kim HJ, Takeda J, Lee YK, Moore DD and Choi HS: Differential regulation of the orphan nuclear receptor SHP gene promoter by orphan nuclear receptor ERR isoforms. *J Biol Chem* 277: 1739-1748, 2002.
- 45 Zhang Z and Teng CT: Estrogen receptor-related receptor alpha 1 interacts with coactivator and constitutively activates the estrogen response elements of the human lactoferrin gene. *J Biol Chem* 275: 20837-20846, 2000.
- 46 Liu D, Zhang Z, Gladwell W and Teng CT: Estrogen stimulates estrogen-related receptor α gene expression through conserved hormone response elements. *Endocrinology* 144: 4894-4904, 2003.
- 47 Bonnelye E, Kung V, Laplace C, Galson DL and Aubin JE: Estrogen receptor-related receptor α impinges on the estrogen axis in bone: potential function in osteoporosis. *Endocrinology* 143: 3658-3670, 2002.
- 48 Huss JM, Kopp RP and Kelly DP: Peroxisome proliferator-activated receptor coactivator-1 α (PGC-1 α) coactivates the cardiac-enriched nuclear receptors estrogen-related receptor- α and- α . Identification of novel leucine-rich interaction motif within PGC-1 α . *J Biol Chem* 277: 40265-40274, 2002.
- 49 Yang C, Zhou D and Chen S: Modulation of aromatase expression in the breast tissue by ERR α -1 orphan nuclear receptor. *Cancer Res* 58: 5695-5700, 1998.
- 50 Vanacker JM, Delmarre C, Guo X and Laudet V: Activation of the osteopontin promoter by the orphan nuclear receptor estrogen receptor related α . *Cell Growth Differ* 9: 1007-1014, 1998.
- 51 Bonnelye E, Merdad L, Kung V and Aubin JE: The orphan nuclear estrogen receptor-related receptor α (ERR α) is expressed throughout osteoblast differentiation and regulates bone formation *in vitro*. *J Cell Biol* 153: 971-984, 2001.

- 52 Horard B, Rayet B, Triqueneaux G, Laudet V, Delaunay F and Vanacker JM: Expression of the orphan nuclear receptor ERR α is under circadian regulation in estrogen-responsive tissues. *J Mol Endocrinol* 33: 87-97, 2004.
- 53 Trapp T and Holsboer F: Nuclear orphan receptor as a repressor of glucocorticoid receptor transcriptional activity. *J Biol Chem* 271: 9879-9882, 1996.
- 54 Susens U, Hermans-Borgmeyer I and Borgmeyer U: Alternative splicing and expression of the mouse estrogen receptor-related receptor gamma. *Biochem Biophys Res Commun* 267: 532-535, 2000.
- 55 Rollerova E and Urbancikova M: Intracellular estrogen receptors, their characterization and function. *Endocr Reg* 34: 203-218, 2000.
- 56 Sanchez R, Nguyen D, Rocha W, White JH and Mader S: Diversity in the mechanisms of gene regulation by estrogen receptors. *Bioessays* 24: 244-254, 2002.
- 57 Russo J, Hu YF, Yang X and Russo IH: Developmental, cellular and molecular basis of human breast cancer. *J Natl Cancer Inst Monogr* 27: 17-37, 2000.
- 58 Ariazi EA, Clark GM and Mertz JE: Estrogen-related receptor α and estrogen-related receptor γ associated with unfavorable and favorable biomarkers, respectively in human breast cancer. *Cancer Res* 62: 6510-6518, 2002.
- 59 Razzaque MA, Masuda N, Maeda Y, Endo Y, Tsukamoto T and Osumi T: Estrogen receptor-related receptor γ has an exceptionally broad specificity of DNA sequence recognition. *Gene* 340: 275-283, 2004.
- 60 Suzuki T, Miki Y, Moriya T, Shimada N, Ishida T, Hirakawa H, Ohuchi N and Sasano H: Estrogen-related receptor α in human breast carcinoma as a potent prognostic factor. *Cancer Res* 64: 4670-4676, 2004.
- 61 Sun P, Sehoul J, Denkert C, Mustea A, Könsgen D, Koch I, Wei L and Lichtenegger W: Expression of estrogen receptor-related receptors, a subfamily of orphan nuclear receptors, as new tumor biomarkers in ovarian cancer cells. *J Mol Med* 83: 457-467, 2005.
- 62 Cheung CP, Yu S, Wong KB, Chan LW, Lai FM, Wang X, Suetsugi M, Chen S and Chan FL: Expression and function study of estrogen receptor-related receptor in human prostatic cells and tissues. *J Clin Endocrin Meta* 90: 1830-1844, 2004.
- 63 Cavallini A, Notarnicola M, Giannini R, Montemurro S, Lorusso D, Visconti A, Minervini F and Caruso MG: Oestrogen receptor-related receptor alpha (ERR α) and oestrogen receptors (ER α and ER β) exhibit different gene expression in human colorectal tumor progression. *Eur J Can* 41: 1487-1494, 2005.
- 64 Chen S, Itoh T, Wu K, Zhou D and Yang C: Transcriptional regulation of aromatase expression in human breast tissue. *J Steroid Biochem Mol Bio* 83: 93-99, 2003.
- 65 Koohi MK, Ivell R and Walther N: Transcriptional activation of the oxytocin promoter by oestrogens uses a novel non-classical mechanism of oestrogen receptor action. *J Neuroendocrinol* 17: 197-207, 2005.

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